

1. A subcollection of samples from a target population, comprising:  
a plurality of samples, wherein the samples are selected from the group  
consisting of blood, tissue, body fluid, cell, seed, microbe, pathogen and  
reproductive tissue samples; and

the target population is a healthy population that has not been selected  
10 for any disease state;

2. The subcollection of claim 1, wherein the parameters are selected from the group consisting of ethnicity, age, gender, height, weight, alcohol intake, number of pregnancies, number of live births, vegetarians, type of physical activity, state of residence and/or length of residence in a particular state, educational level, age of parent at death, cause of parent death, former or current smoker, length of time as a smoker, frequency of smoking, occurrence of a disease in immediate family (parent, siblings, children), use of prescription drugs and/or reason therefor, length and/or number of hospital stays and exposure to environmental factors.

25 *Sub D2* } 4. A method of producing a database, comprising:  
identifying healthy members of a population;  
obtaining data comprising identifying information and obtaining historical  
information and data relating to the identified members of the population and  
their immediate family;

5. The method of claim 4, further comprising:  
obtaining a body tissue or body fluid sample;

analyzing the body tissue or body fluid in the sample; and  
entering the results of the analysis for each member into the database  
and associating each result with the indexer representative of each member.

6. A database produced by the method of claim 4.

5 7. A database produced by the method of claim 5.

8. A database, comprising:

Sub D3 } datapoints representative of a plurality of healthy organisms from  
whom biological samples are obtained,

10 wherein each datapoint is associated with data representative of  
the organism type and other identifying information.

9. The database of claim 8, wherein the datapoints are answers to  
questions regarding one or more of a parameters selected from the group  
consisting of ethnicity, age, gender, height, weight, alcohol intake, number of  
pregnancies, number of live births, vegetarians, type of physical activity, state of  
15 residence and/or length of residence in a particular state, educational level, age  
of parent at death, cause of parent death, former or current smoker, length of  
time as a smoker, frequency of smoking, occurrence of a disease in immediate  
family (parent, siblings, children), use of prescription drugs and/or reason  
therefor, length and/or number of hospital stays and exposure to environmental  
20 factors.

10. The database of claim 9, wherein the organisms are mammals and  
the samples are body fluids or tissues.

11. The database of claim 9, wherein the samples are selected from  
blood, blood fractions, cells and subcellular organelles.

25 12. The database of claim 8, further comprising,  
phenotypic data from an organism.

13. The database of claim 12, wherein the data includes one of physical  
characteristics, background data, medical data, and historical data.

30 14. The database of claim 8, further comprising,  
genotypic data from nucleic acid obtained from an organism.

16. The database of claim 8 that is a relational database.

18. A method of identifying polymorphisms that are candidate genetic markers, comprising:

the polymorphisms are identified in samples associated with a target population that comprises healthy subjects.

a) hybridizing a first oligonucleotide to the target nucleic acid;

b) hybridizing a second oligonucleotide to an adjacent region of the target nucleic acid;

20. The method of claim 18, wherein the polymorphism is identified by detecting target nucleic acids in a sample by a method, comprising the steps of:

b) contacting the hybridized first and second oligonucleotides with a cleavage enzyme to form a cleavage product; and

- 119 -

21. The method of claim 20 wherein the samples are from subjects in a healthy database.

22. The method of claim 18, wherein the polymorphism is identified by identifying target nucleic acids in a sample by primer oligo base extension  
5 (probe).

23. The method of 22, wherein primer oligo base extension, comprises:

- a) obtaining a nucleic acid molecule that contains a target nucleotide;
- b) optionally immobilizing the nucleic acid molecule onto a solid support,  
10 to produce an immobilized nucleic acid molecule;
- c) hybridizing the nucleic acid molecule with a primer oligonucleotide that is complementary to the nucleic acid molecule at a site adjacent to the target nucleotide;
- d) contacting the product of step c) with a composition comprising a  
15 dideoxynucleoside triphosphate or a 3'-deoxynucleoside triphosphates and a polymerase, so that only a dideoxynucleoside or 3'-deoxynucleoside triphosphate that is complementary to the target nucleotide is extended onto the primer; and
- e) detecting the extended primer, thereby identifying the target nucleotide.

20 24. The method of claim 23, wherein detection of the extended primer is effected by mass spectrometry, comprising:  
ionizing and volatilizing the product of step d) ; and  
detecting the extended primer by mass spectrometry, thereby identifying the target nucleotide.

25 25. The method of claim 24, wherein;  
samples are presented to the mass spectrometer as arrays on chips; and  
each sample occupies a volume that is about the size of the laser spot projected by the laser in a mass spectrometer used in matrix-assisted laser desorption/ionization (MALDI) spectrometry.

26. A combination, comprising:  
a database containing parameters associated with a datapoint  
representative of a subject from whom samples are obtained, wherein the  
subjects are healthy; and

27 The combination of claim 26, wherein the parameter is selected  
from the group consisting of ethnicity, age, gender, height, weight, alcohol  
intake, number of pregnancies, number of live births, vegetarians, type of  
10 physical activity, state of residence and/or length of residence in a particular  
state, educational level, age of parent at death, cause of parent death, former or  
current smoker, length of time as a smoker, frequency of smoking, occurrence  
of disease in immediate family (parent, siblings, children), use of prescription  
drugs and/or reason therefor, length and/or number of hospital stays and  
15 exposure to environmental factors.

28. The combination of claim 26, wherein the database further contains genotypic data for each subject.

29. The combination of claim 26, wherein the samples are blood.

30 A data storage medium, comprising the database of claim 8.

20            31.     A computer system, comprising the database of claim 8.

32. A system for high throughput processing of biological samples, comprising:

25 a process line comprising a plurality of processing stations, each of which performs a procedure on a biological sample contained in a reaction vessel;

a robotic system that transports the reaction vessel from processing station to processing station;

30 a data analysis system that receives test results of the process line and  
automatically processes the test results to make a determination  
regarding the biological sample in the reaction vessel;

a control system that determines when the test at each processing station is complete and, in response, moves the reaction vessel to

5

10

15

20

25

30

38. The method of claim 37, further comprising:

5 spectrometer such that the test data for a biological sample contains one or more signals or numerical values representative of signals, whereupon the data analysis system determines the area under the curve of each signal and normalizes the results thereof and obtains a substantially quantitative result representative of the relative amounts of components in the tested sample.

a) obtaining a nucleic acid molecule that contains a target nucleotide;  
b) optionally immobilizing the nucleic acid molecule onto a solid support,  
to produce an immobilized nucleic acid molecule;

d) contacting the product of step c) with composition comprising a dideoxynucleoside triphosphate or a 3'-deoxynucleoside triphosphates and a polymerase, so that only a dideoxynucleoside or 3'-deoxynucleoside triphosphate that is complementary to the target nucleotide is extended onto the primer; and

e) detecting the primer, thereby identifying the target nucleotide.

25 ionizing and volatilizing the product of step d); and  
detecting the extended primer by mass spectrometry, thereby identifying  
the target nucleotide.

30      a)      hybridizing a first oligonucleotide to the target nucleic acid;  
              b)      hybridizing a second oligonucleotide to an adjacent region of the  
              target nucleic acid;

42. The method of claim 36, wherein the target nucleic acids in the sample are detected and/or identified by a method, comprising the steps of:

b) ~~contacting the hybridized first and second oligonucleotides with a~~  
cleavage enzyme to form a cleavage product; and

43. A method of producing a database stored in a computer memory, comprising:

- identifying healthy members of a population;
- obtaining identifying and historical information and data relating to the identified members of the population;
- entering the member-related data into the computer memory database for each identified member of the population and associating the member and the data with an indexer.

44. The method of claim 43, further comprising:  
obtaining a body tissue or body fluid sample of an identified member;  
analyzing the body tissue or body fluid in the sample; and  
entering the results of the analysis for each member into the computer  
memory database and associating each result with the indexer representative of  
each member.

45. A database produced by the method of claim 43.

46. A database produced by the method of claim 44.

47. The database of claim 8, wherein:  
the organisms are selected from among animals, bacteria, fungi,  
protozoans and parasites and



48. The database of claim 43, further comprising, phenotypic data regarding each subject.

50. The database of claim 8, further comprising,  
genotypic data of nucleic acid of the subject, wherein genotypic data  
includes, but is not limited to, genetic markers, non-coding regions,  
10 microsatellites, restriction fragment length polymorphisms (RFLPs), variable  
number tandem repeats (VNTRs), historical day of the organism, the medical  
history of the subject, phenotypic information, and other information.

52. The database of claim 51, further comprising an index value for each identified member that associates each member of the population with the identifying and historical information and data.

54. An automated process line, comprising the database of claim 51.

55. A method for determining a polymorphism that correlates with age, ethnicity or gender, comprising:

identifying a polymorphism; and

25 determining the frequency of the polymorphism with increasing age, with ethnicity or with gender in a healthy population.

56. A method for determining whether a polymorphism correlates with susceptibility to morbidity, early mortality, or morbidity and early mortality, comprising;

30 identifying a polymorphism; and  
determining the frequency of the polymorphism with increasing age in a  
healthy population.

selecting a healthy target population and a genetic variation to be assessed;

determining or detecting the biopolymer that comprises the variation by mass spectrometry;

58. The method of claim 57, wherein:

15 the biopolymer is a nucleic acid, a protein, a polysaccharide, a lipid, a  
small organic metabolite or intermediate, wherein the concentration of  
biopolymer of interest is the same in each of the samples; and/or

59. The method of claim 58, wherein the method for determining the frequency is effected by determining the ratio of the signal or the digital representation thereof to the total area of the entire mass spectrum, which is corrected for background.

sorting the database of claim 8 according to a selected parameter to identify samples that match the selected parameter;

30 isolating a biopolymer from each identified sample;  
optionally pooling each isolated biopolymer;  
optionally amplifying the amount of biopolymer;

obtaining a mass spectrum of the resulting fragments and comparing the mass spectrum with a control mass spectrum to identify differences between the spectra and thereby identifying any polymorphisms; wherein:

61. The method of claim 60, wherein cleaving is effected by contacting the biopolymer with an enzyme.

63. The method of claim 60, wherein the biopolymer is a nucleic acid or a protein.

65. A method for discovery of a polymorphism in a population, comprising:

66. The method of claim 65, wherein cleaving is effected by contacting the biopolymer with an enzyme.

67. The method of claim 66, wherein the enzyme is selected from the group consisting of nucleotide glycosylase, a nickase and a type IIS restriction enzyme.

68. The method of claim 65, wherein the biopolymer is a nucleic acid or a protein.

69. The method of claim 65, wherein the mass spectrometric format is selected from among Matrix-Assisted Laser Desorption/Ionization, Time-of-Flight (MALDI-TOF), Electrospray (ES), IR-MALDI, Ion Cyclotron Resonance (ICR), Fourier Transform and combinations thereof.

70. The method of claim 65, wherein the samples are obtained from healthy subjects.

71. A method of correlating a polymorphism with a parameter, comprising:

sorting the database of claim 8 according to a selected parameter to identify samples that match the selected parameter;

isolating a biopolymer from each identified sample;

pooling each isolated biopolymer;

optionally amplifying the amount of biopolymer;

determining the frequency of the polymorphism in the pooled biopolymers, wherein:

an alteration of the frequency of the polymorphism compared to a control, indicates a correlation of the polymorphism with the selected parameter; and

the control is the frequency of the polymorphism in pooled biopolymers obtained from samples identified from an unsorted database or from a database sorting according to a different parameter.

72. The method claim 71, wherein the parameter is selected from the group consisting of ethnicity, age, gender, height, weight, alcohol intake, number of pregnancies, number of live births, vegetarians, type of physical activity, state of residence and/or length of residence in a particular state, educational level, age of parent at death, cause of parent death, former or current smoker, length of time as a smoker, frequency of smoking, occurrence of a disease in immediate family (parent, siblings, children), use of prescription

drugs and/or reason therefor, length and/or number of hospital stays and exposure to environmental factors.

73. The method claim 72, wherein the parameter is occurrence of disease or a particular disease in an immediate family member, thereby correlating the polymorphism with the disease.

74. The method of claim 71, wherein the pooled biopolymers are pooled nucleic acid molecules.

75. The method of claim 74, wherein the polymorphism is detected by primer oligo base extension (PROBE).

76. The method of 75, wherein primer oligo base extension, comprises:

a) optionally immobilizing the nucleic acid molecules onto a solid support, to produce immobilized nucleic acid molecules;

b) hybridizing the nucleic acid molecules with a primer oligonucleotide that is complementary to the nucleic acid molecule at a site adjacent to the polymorphism;

c) contacting the product of step c) with composition comprising a dideoxynucleoside triphosphate or a 3'-deoxynucleoside triphosphates and a polymerase, so that only a dideoxynucleoside or 3'-deoxynucleoside triphosphate that is complementary to the polymorphism is extended onto the primer; and

d) detecting the extended primer, thereby detecting the polymorphism in nucleic acid molecules in the pooled nucleic acids.

77. The method of claim 76, wherein detecting is effected by mass spectrometry.

78. The method of claim 71, wherein the frequency is percentage of nucleic acid molecules in the pooled nucleic acids that contain the polymorphism.

79. The method of claim 78, wherein the ratio is determined by obtaining mass spectra of the pooled nucleic acids.

80. The method of claim 72, wherein the parameter is age, thereby correlating the polymorphism with susceptibility to morbidity, early mortality or morbidity and early mortality.

(a) sorting the database of claim 8 according to a selected parameter to identify samples that match the selected parameter;

(c) optionally pooling each isolated nucleic acid;

(e) forming single-stranded nucleic acid and splitting each single- into a separate reaction vessel;

(g) contacting the adaptor complex with a nuclease and a ligase;

15 (i) obtaining a mass spectrum of each nucleic acid resulting from step (h) and detecting a polymorphism by identifying a signal corresponding to the extended product;

(j) repeating steps (f) through (i) utilizing an adaptor nucleic acid able to hybridize with another adaptor nucleic acid that hybridizes to a different target nucleic acid.

the polymorphisms are haplotyped by detecting more than one extended  
ct.

83. A method for haplotyping polymorphisms in a population,

sorting the database of claim 8 according to a selected parameter to  
y samples that match the selected parameter;

pooling each isolated nucleic acid;

contacting the nucleic acid with at least one enzyme to produce  
agents thereof;

the polymorphisms are haplotyped by determining from the mass spectrum that the polymorphisms are located on the same strand of the nucleic acid.

85. The method of claim 84, wherein the nickase is selected from the

splitting a nucleic acid sample into separate reaction vessels;  
contacting nucleic acid in one reaction vessel with bisulfite;  
amplifying the nucleic acid in each reaction vessel;  
cleaving the nucleic acids in each reaction vessel to produce fragments thereof;

20 cytosine methylation is detected by identifying a difference in signals  
between the mass spectra.

the step of amplifying is carried out in the presence of uracil; and the step of cleaving is effected by a uracil glycosylase.

-131-





identifying, using the located probable peak, the biological sample;  
 wherein identifying includes deriving a peak probability for the probable  
 peak and

applying an allelic penalty in response to a ratio between a calculated  
 5 area under the probable peak and a calculated expected average area under all  
 peaks in the data set.

93. The method according to claim 92, wherein identifying includes  
 comparing data from probable peaks that did not receive an applied allelic  
 penalty to determine their mass in accordance with oligonucleotide biological  
 10 data.

94. The method according to claim 92, wherein the allelic penalty is  
 not applied to probable peaks whose ratio of area under the peak to the  
 expected area value is greater than 30%.

95. A method for detecting a polymorphism in a nucleic acid,  
 15 comprising:

amplifying a region of the nucleic acid to produce an amplicon, wherein  
 the resulting amplicon comprises one or more enzyme restriction sites;  
 contacting the amplicon with a restriction enzyme to produce fragments;  
 obtaining a mass spectrum of the resulting fragments and analyzing  
 20 signals in the mass spectrum by the method of claim 88; whereby:  
 the polymorphism is detected from the pattern of the signals.

96. A subcollection of samples from a target population, comprising:  
 a plurality of samples, wherein the samples are selected from the group  
 consisting of nucleic acids, fetal tissue, protein samples; and  
 25 a symbology on the containers containing the samples, wherein the  
 symbology is representative of the source and/or history of each sample,  
 wherein:

the target population is a healthy population that has not been selected  
 for any disease state;  
 30 the collection comprises samples from the healthy population; and  
 the subcollection is obtained by sorting the collection according to  
 specified parameters.

~~combinat  
group cou  
ed, micro~~

5

analyzing biological samples.

Sub

10